awaiting results of resistance testing (see **Antiretroviral Drug Resistance and Resistance Testing in Pregnancy**).

The importance of adherence to the antiretroviral treatment or prophylaxis regimen should be emphasized. Depending on individual circumstances, provision of support services, mental health services, and drug abuse treatment may be required. Coordination of services among prenatal care providers, primary care and HIV specialty care providers, mental health and drug abuse treatment services, and public assistance programs is essential to ensure adherence of the infected woman to the antiretroviral treatment regimen. Long-range plans should be developed with the woman regarding continuity of medical care and decisions about antiretroviral therapy for her own health after the birth of her infant.

Medical care of the HIV-infected pregnant woman requires coordination and communication between HIV specialists and obstetrical providers. General counseling should include current knowledge regarding risk factors for perinatal transmission. Potentially modifiable factors including cigarette smoking, illicit drug use, genital tract infections, and unprotected sexual intercourse with multiple partners during pregnancy have been associated with risk of perinatal HIV transmission *[4-8]*. In addition to improving maternal health, cessation of cigarette smoking and drug use, treatment of genital tract infections, and use of condoms with sexual intercourse during pregnancy may reduce risk of perinatal transmission. In addition, the CDC recommends that HIV-infected women in the United States (including those receiving antiretroviral therapy) refrain from breastfeeding to avoid postnatal transmission of HIV to their infants through breast milk *[9]*.

The National Perinatal HIV Hotline (1-888-448-8765)

The National Perinatal HIV Hotline is a federally funded service providing free clinical consultation to providers caring for HIV-infected women and their infants.

RECOMMENDATIONS FOR USE OF ANTIRETROVIRAL DRUGS DURING PREGNANCY

The Panel recommends that choice of antiretroviral drug regimens for HIV-infected pregnant women be based on the same principles used to choose regimens for non-pregnant individuals, unless there are compelling pregnancy-specific maternal or fetal safety issues regarding specific drug choices. The Panel reviews clinical trial data published in peer-reviewed journals and data prepared by manufacturers for FDA review related to treatment of HIV-infected adult women, both pregnant and nonpregnant. The durability, tolerability, and simplicity of the medication regimen is of particular importance in order to preserve options in the future for those women who will be stopping medications following delivery and for those women who meet standard criteria for initiation of antiretroviral therapy per adult guidelines and will continue the regimen after pregnancy. Regimen selection should be individualized and should consider a number of factors including:

- comorbidities,
- patient adherence potential,
- convenience,
- potential adverse drug effects on the mother,
- potential drug interactions with other medications,
- results of genotypic resistance testing,
- pharmacokinetic (PK) changes in pregnancy, and
- potential teratogenic effects on the fetus and other adverse effects on the fetus or newborn.

Criteria used by the Panel for recommending specific drugs or regimens for pregnant women include:

- Data from randomized prospective clinical trials that demonstrate durable viral suppression as well as immunologic and clinical improvement;
- Incidence rates and descriptions of short- and long-term drug toxicity of antiretroviral regimens with special attention to maternal toxicity and safety and teratogenic effects on the fetus;
- Specific knowledge about drug tolerability and simplified dosing regimens;
- Drug regimens that are known to be effective in reducing transmission to the fetus;
- Pharmacokinetic data during the prenatal period: The physiologic changes of pregnancy have the potential to alter the pharmacokinetics of drugs. Antiretroviral dosing during pregnancy should be based on pharmacokinetic data from studies in pregnant women. Physiologic changes are not fixed throughout pregnancy but rather reflect a continuum of change as pregnancy progresses, with return to baseline at various rates in the postpartum period.

Categories of antiretroviral regimens include:

- ***Preferred:*** Drugs or drug combinations are designated as preferred for use in pregnant women when clinical trial data in adults have demonstrated optimal efficacy and durability with acceptable toxicity and ease of use; pregnancy-specific pharmacokinetic data are available to guide dosing; and no evidence of teratogenic effects on the fetus or established association with teratogenic or clinically significant adverse outcomes for the mother, fetus, or newborn are present.

- ***Alternative:*** Drugs or drug combinations are designated as alternatives for initial therapy in pregnant women when clinical trial data in adults show efficacy but any one or more of the following conditions apply: there is limited experience in pregnancy; there is lack of data on teratogenic effects on the fetus; or there are dosing, formulation, administration, or interaction issues for that drug or regimen.

- ***Use in Special Circumstances:*** Drug or drug combinations in this category can be considered for use when intolerance or resistance prohibits use of other drugs with fewer toxicity concerns or the woman has comorbidities or requires concomitant medications that may limit drug choice (e.g., chronic hepatitis B infection, active tuberculosis requiring rifampin therapy).

- ***Not Recommended:*** Drugs and drug combinations listed in this category are not recommended for therapy in pregnant women because of inferior virologic response, potential serious safety concerns for the mother or fetus, or pharmacologic antagonism.

- ***Insufficient Data to Recommend:*** Although approved for use in adults, the drugs and drug combinations in this category do not have pregnancy-specific pharmacokinetic or safety data available or such data are too limited to make a recommendation for use for pregnancy.

All women who receive antiretroviral drugs during pregnancy either for treatment or prophylaxis should receive combination regimens containing at least three agents. A combination regimen including two nucleoside reverse transcriptase inhibitors (NRTIs) and either a non-nucleoside reverse transcriptase inhibitor (NNRTI) or a protease inhibitor (PI) (with or without low-dose ritonavir) should be used. The preferred NRTI regimen in pregnancy, based on efficacy studies in preventing perinatal transmission (see **Lessons from Clinical Trials of Antiretroviral Interventions to Reduce Perinatal HIV Transmission**) and large experience with use in pregnancy, is zidovudine/lamivudine. Alternate regimens may be used for women who have intolerance of zidovudine because of toxicity such as severe anemia or with known resistance to zidovudine. Tenofovir, a preferred NRTI in nonpregnant women, should be used only in special circumstances (such as intolerance or resistance to zidovudine or chronic hepatitis B infection) because of concerns regarding the potential for fetal toxicity. Animal studies have shown decreased fetal growth and reduction in fetal bone porosity, and studies in infected children on chronic tenofovir-based therapy have shown bone demineralization in some children. The combination of stavudine/didanosine should not be used in pregnant women because of fatal cases of lactic acidosis and hepatic failure reported in pregnant women who received this combination throughout pregnancy.

In addition to the two NRTIs, either an NNRTI or a PI should be included in antiretroviral regimens prescribed for maternal health. Efavirenz, the preferred NNRTI for nonpregnant adults, is not recommended for use in the first trimester of pregnancy because of animal data showing risk of anencephaly, micro-ophthalmia, and facial clefts as well as concerning case reports of several neural tube defects and a single case of anophthalmia with severe facial cleft in humans. Use of efavirenz after the first trimester of pregnancy may be considered if alternate agents are not tolerated. Nevirapine may be used in women with CD4+ lymphocyte counts less than 250 cells/mm^3 or continued for women already receiving a nevirapine-based regimen. Nevirapine should generally not be initiated for treatment-naïve women with CD4+ cell counts greater than 250 cells/mm^3 because of an increased risk of symptomatic and potentially fatal rash and hepatic toxicity. Etravirine has insufficient safety or pharmacokinetic data in pregnancy to recommend its use. Lopinavir/ritonavir is the preferred protease inhibitor regimen for pregnant women because of efficacy studies in adults and experience with use in pregnancy (see **Table 5** for dosing considerations). Alternative protease inhibitors include ritonavir-boosted atazanavir, saquinavir, or indinavir, although experience with these regimens in pregnancy is more limited and the latter two may be less well tolerated. Data on use in pregnancy for darunavir, fosamprenavir, and tipranavir are too limited to recommend routine use in pregnancy, although they may be considered if other agents are not tolerated.

Safety and pharmacokinetics data in pregnancy are insufficient to recommend use of the entry inhibitors enfuvirtide and maraviroc and the integrase inhibitor raltegravir during pregnancy. Use of these agents for women who have failed therapy with several other classes of antiretroviral drugs could be considered in consultation with HIV and obstetric specialists.

In addition, recommendations for the use of antiretroviral drugs for prophylaxis to prevent perinatal HIV transmission in women for whom therapy would not otherwise be indicated include the agents/combinations discussed above and some that are not considered preferred regimens in nonpregnant adults, such as triple NRTI regimens with abacavir and the use of nelfinavir with two NRTIs. These options are discussed in more detail below.

Although data are insufficient to support or refute the teratogenic risk of antiretroviral drugs when administered during the first 10 weeks of gestation, information to date does not support major teratogenic effects of the majority of antiretroviral drugs. (For further data, see **www.APRegistry.com**.) However, certain drugs are of more concern than others (**Table 4** and see **Teratogenicity** and **Supplement: Safety and Toxicity of Individual Antiretroviral Drugs in Pregnancy**). For example, efavirenz should be avoided during the first trimester of pregnancy.

Recommendations for antiretroviral therapy during pregnancy must be individualized according to the specific antiretroviral history of the HIV-infected pregnant woman. Some women may be receiving antiretroviral therapy for their own health at the time they become pregnant and present for obstetrical care on such therapy. Other HIV-infected women may not be receiving antiretroviral therapy at the time they present for obstetrical care. Some of these women have never received antiretroviral drugs before, while other women may have previously received antiretroviral drugs, either for treatment that was stopped or for prophylaxis to prevent perinatal HIV transmission in prior pregnancies. Considerations for initiating therapy will differ for such women according to whether antiretroviral drugs are currently indicated for maternal health or solely for fetal protection. The antiretroviral recommendations below are divided into sections according to antiretroviral treatment status at the time the woman presents for care and whether there are maternal indications for therapy.

Table 5 provides recommendations about the use of specific antiretroviral drugs in pregnancy as well as data on pharmacokinetics and toxicity in pregnancy. **Table 6** provides a summary of management recommendations for the mother and infant in a variety of clinical scenarios.

HIV-Infected Pregnant Women Who Are Currently Receiving Antiretroviral Treatment

Panel's Recommendations:

- ***Pregnant women receiving and tolerating an antiretroviral treatment regimen that is currently effective in suppressing viral replication should continue on the regimen; however, the use of efavirenz should be avoided in the first trimester of pregnancy (AIII).***
- ***HIV antiretroviral drug resistance testing is recommended if the pregnant woman has detectable viremia (e.g., >500–1,000 copies/mL) on therapy (see Failure of Viral Suppression) (AI).***
- ***Pregnant women receiving nevirapine-containing regimens who are virologically suppressed and tolerating the regimen should continue the regimen, regardless of CD4 count (AIII).***

In general, women who have been receiving antiretroviral treatment for their HIV infection should continue treatment during pregnancy. Discontinuation of therapy could lead to an increase in viral load with possible decline in immune status and disease progression as well as adverse consequences for the fetus, including increased risk of HIV transmission. Therefore, when pregnancy is identified after the first trimester in HIV-infected women receiving antiretroviral therapy at the time of conception, therapy should always be continued.

HIV-infected women receiving antiretroviral treatment who present for care during the first trimester of pregnancy should be counseled regarding the benefits and potential risks of antiretroviral administration during this period, and continuation of therapy should be recommended. However, the use of efavirenz should be avoided during the first trimester of pregnancy. If a woman is receiving efavirenz and her pregnancy is recognized during the first trimester, an alternative antiretroviral drug should be substituted when possible (see **Monitoring of the Woman and Fetus during Pregnancy**).

Resistance testing should be performed in women who are on therapy but not fully suppressed. Results of this testing can be used to select a regimen that may have greater chance to suppress viral loads to undetectable. It should be noted that resistance assays vary depending on the HIV RNA level required to detect resistance mutations. Some assays require HIV RNA levels of ≥1,000 copies/mL; other assays can be performed with lower viral loads.

Pregnant women who are receiving nevirapine-containing regimens with viral suppression and are tolerating the regimen well should continue therapy, regardless of CD4 count. Although hepatic toxicity is a concern in women who have a CD4 count >250 cells/mm^3 when they first start a nevirapine-containing regimen, an increased risk of hepatic toxicity has not been seen in women who are receiving nevirapine-based therapy and have immune reconstitution with therapy.

HIV-Infected Pregnant Women Who Have Never Received Antiretroviral Drugs (Antiretroviral Naïve)

Panel's Recommendations:

- ***HIV-infected pregnant women who meet standard criteria for initiation of antiretroviral therapy per adult antiretroviral treatment guidelines should receive standard potent combination antiretroviral therapy as recommended for nonpregnant adults, taking into account what is known about the use of specific drugs in pregnancy and risk of teratogenicity (Table 5) (AI).***
  - ***For women who require immediate initiation of therapy for their own health, treatment should be started as soon as possible, including in the first trimester of pregnancy (AII). (Note that the use of efavirenz should be avoided during the first trimester.)***
- ***HIV-infected pregnant women who do not require treatment for their own health should also receive three-drug combination antiretroviral regimens for prophylaxis of perinatal transmission (AII). The use of zidovudine alone as prophylaxis is controversial but may be considered for those women initiating prophylaxis with plasma HIV RNA levels <1,000 copies/mL on no therapy (CII).***
  - ***For women who are receiving antiretroviral drugs solely for prevention of perinatal transmission, delaying initiation of prophylaxis until after the first trimester of pregnancy can be considered (BIII).***
- ***Zidovudine should be used as a component of the antiretroviral regimen when feasible (AIII).***
- ***HIV antiretroviral drug resistance testing should be performed prior to initiating antiretroviral prophylaxis or therapy (AI)*.***
- ***Nevirapine may be used as a component of initial therapy for pregnant women with CD4 cell counts <250 cells/mm^3. However, due to an increased risk of hepatic toxicity, nevirapine should only be used as a component of antiretroviral therapy in pregnant women with CD4 cell counts >250 cells/mm^3 if the benefit clearly outweighs the risk (AII).***

**Dependent on the resistance assay being used; some assays require HIV RNA levels of ≥1,000 copies/mL for performance of the resistance assay, while other assays can be used with lower levels of viral replication.*

Pregnant women with HIV infection should receive standard clinical, immunologic, and virologic evaluation. Decisions about the need for initiation of therapy should be based on the standard guidelines for nonpregnant adults *[10]*.

HIV-Infected Pregnant Women Not on Antiretroviral Therapy and Who Need Antiretroviral Treatment for Their Own Health

Any HIV-infected pregnant woman who meets standard criteria for initiation of antiretroviral therapy as per adult antiretroviral guidelines should receive potent combination antiretroviral therapy, generally consisting of NRTIs plus an NNRTI or PIs, with continuation of therapy postpartum. For women who require immediate initiation of therapy for their own health, treatment should be started as soon as possible, including in the first trimester, because the potential benefit of treatment for the mother outweighs potential fetal risks. The regimen should generally be chosen from those recommended for nonpregnant adults (e.g., a preferred or alternative regimen), taking into account what is known about use of the drugs during pregnancy and risk of teratogenicity (see **Table 5** and **Teratogenicity**) *[10]*.

Women with CD4 counts >250 cells/mm^3 have an increased risk of developing symptomatic, often rash-associated, nevirapine-related hepatotoxicity that can be severe, life-threatening, and in some cases fatal *[11-12]*. Therefore, nevirapine should only be used as a component of a combination regimen when antiretroviral therapy is being initiated in women with CD4 counts >250 cells/mm^3 if the benefit clearly outweighs the risk. If nevirapine is used, frequent and careful monitoring of

transaminase levels, particularly during the first 18 weeks of treatment, is required (see **Nevirapine and Hepatic/Rash Toxicity**). Transaminase levels should be checked in all women who develop a rash while receiving nevirapine. Nevirapine should be stopped immediately in all women who develop signs or symptoms of hepatitis.

HIV-Infected Pregnant Women Not on Antiretroviral Therapy Who Require Antiretroviral Prophylaxis Solely to Prevent Perinatal HIV Transmission

HIV-infected pregnant women should be counseled regarding the benefits of antiretroviral drugs for prevention of perinatal transmission even when initiation of antiretroviral therapy for maternal health is not recommended or is considered optional on the basis of current guidelines for treatment of nonpregnant persons *[10]*. Although such women are at low risk of clinical disease progression if antiretroviral treatment is delayed, use of an antiretroviral regimen that successfully reduces plasma HIV RNA to undetectable levels substantially lowers the risk of perinatal HIV transmission and lessens the need for consideration of elective cesarean delivery as an intervention to reduce transmission risk.

Because the fetus is most susceptible to the potential teratogenic effects of drugs during the first 10 weeks of gestation and the risks of antiretroviral therapy during that period are not fully known, women in the first trimester of pregnancy who do not require immediate initiation of therapy for their own health may consider delaying initiation until after 10 to 12 weeks gestation. This decision should be carefully considered by the health care provider and the woman; a discussion should include an assessment of the woman's health status, the benefits and risks to her of delaying initiation of therapy for several weeks, and the fact that most perinatal HIV transmission likely occurs late in pregnancy or during delivery.

Antiretroviral prophylaxis is recommended for all pregnant women with HIV infection, regardless of viral load. Although rates of perinatal transmission are low in women with undetectable or low HIV RNA levels (e.g., <1,000 copies/mL), there is no threshold below which lack of transmission can be assured *[2, 13-14]*. The mechanism by which antiretroviral drugs reduce perinatal HIV transmission is multifactorial. Although lowering maternal antenatal viral load is an important component of prevention in women with higher viral load, antiretroviral prophylaxis is effective even in women with low viral load *[15-19]*. Additional mechanisms of protection include pre-exposure prophylaxis of the infant, provided by passage of the antiretroviral drug across the placenta so that inhibitory levels of drug are present in the fetus particularly during the birth process, and post-exposure prophylaxis through continued administration to the infant. Although placental passage of zidovudine is excellent, that of many other antiretroviral drugs may be variable (**Table 4**). Therefore, when combination antiretroviral therapy is initiated during pregnancy, zidovudine should be included as a component of antenatal therapy whenever possible. If antenatal zidovudine use is not possible, at least one agent with known transplacental passage should be part of the antiretroviral regimen (see **Table 4**).

Combination antiretroviral regimens containing at least three drugs for prevention of perinatal HIV transmission should be discussed and offered to all pregnant women with HIV infection. A number of studies suggest that antenatal use of combination antiretroviral regimens further reduces transmission compared to use of zidovudine alone. In a longitudinal epidemiologic study conducted in the United States since 1990, transmission was observed in 20% of women with HIV infection who received no antiretroviral treatment during pregnancy, 10.4% who received zidovudine alone, 3.8% who received combination therapy without protease inhibitors (primarily dual NRTIs), and 1.2% who received combination therapy with protease inhibitors *[2]*. However, in these older studies, zidovudine alone was often used in women with higher viral load and lower CD4, in whom treatment would now be recommended. In more recent data from the United Kingdom and Ireland, perinatal transmission occurred among 9.1% of women who received no antiretroviral drugs, 0.5% of women who received single drug prophylaxis (primarily zidovudine, as recommended by U.K. guidelines for women with HIV RNA levels less than 10,000 copies/mL), 0.8% of women who received dual drug prophylaxis,

and 1.0% of women who received triple drug regimens for treatment or prophylaxis. There were no significant differences in transmission rate between the drug regimen groups; the majority of women in all groups were delivered by scheduled cesarean delivery. Among 2,117 infants born to women on triple drug combination antiretroviral therapy or prophylaxis with HIV RNA less than 50 copies/mL at delivery, only 0.1% were infected *[20]*.

A three-drug combination antiretroviral regimen not regarded as one of the standard first-line regimens recommended for adults who require therapy may be considered for the pregnant woman if the regimen is given solely to reduce perinatal transmission, is only needed because the woman is pregnant, and will be discontinued postpartum. The triple NRTI combination zidovudine/lamivudine/abacavir regimen may be considered because of known pharmacokinetic profiles and published data suggesting acceptable toxicities during pregnancy. Testing for HLA-B*5701 identifies patients at risk of hypersensitivity reactions *[21-22]* and should be done and documented as negative before starting abacavir. Triple drug regimens containing the PI nelfinavir, which is not part of standard first-line therapy, may also be considered because there is a large experience with its safe use during pregnancy. However, these regimens have inferior long-term virologic efficacy, and for women with high CD4 counts but high viral load (i.e., CD4 count >350/mm^3 and HIV RNA >100,000 copies/mL), the use of first-line, more potent regimens should be considered. Dual NRTI therapy without the addition of a third drug (i.e., a PI, NNRTI, or a third NRTI) is not recommended because of the potential for inadequate viral suppression and rapid development of resistance *[10, 23]*.

The time-limited use of zidovudine alone during pregnancy for chemoprophylaxis against perinatal transmission is controversial. However, some women who may wish to restrict exposure of their fetus to antiretroviral drugs during pregnancy while still reducing the risk of transmitting HIV to their infants may opt for use of zidovudine alone. Additionally, for women with low viral load, time-limited use of zidovudine during the second and third trimesters of pregnancy is less likely to induce the development of resistance than in women with higher viral loads because of the low level of viral replication in the virologically suppressed women and the short duration of exposure to the antiretroviral drug *[24-25]*. For example, the development of zidovudine resistance was unusual among the healthy population of women who participated in PACTG 076 *[26]*. Thus, although controversial, the use of zidovudine chemoprophylaxis alone during pregnancy might be an appropriate option for this subset of women (i.e., women with HIV RNA levels <1,000 on no treatment).

In general, if antiretroviral drugs are given solely for prevention of perinatal HIV transmission, the antiretroviral drugs are discontinued postnatally, with the option to reinitiate standard potent treatment regimens in the future according to the usual criteria for nonpregnant individuals. Discussion regarding the decision to continue or stop antiretrovirals postpartum should occur before beginning antiretrovirals during pregnancy. Generally, when drugs are discontinued postnatally, all drugs should be stopped simultaneously. However, as discussed later (see **Stopping Antiretroviral Therapy during Pregnancy**), in women receiving NNRTI-based regimens, continuing the dual NRTI backbone for a period of time after stopping the NNRTI should be considered to reduce the development of NNRTI resistance. An alternative strategy is to replace the NNRTI with a PI drug while continuing the NRTIs, then to discontinue all the drugs at the same time *[27]*. The optimal interval between stopping an NNRTI and the other antiretroviral drugs is not known; at least 7 days is recommended. In patients receiving an efavirenz-based NNRTI regimen after the first trimester, detectable drug concentrations may be observed for more than 3 weeks after stopping efavirenz. Therefore, some experts recommend continuing the other antiretroviral agents or substituting a PI plus two other agents for up to 30 days in such patients.

HIV-Infected Pregnant Women Who Have Previously Received Antiretroviral Treatment or Prophylaxis but Are Not Currently Receiving Any Antiretroviral Medications

Panel's Recommendations:

- ***Obtain an accurate history of all prior antiretroviral regimens used for treatment of HIV disease or prevention of transmission and results of prior resistance testing (AIII).***
- ***Perform HIV antiretroviral drug resistance testing prior to initiating repeat antiretroviral prophylaxis or therapy (AI).***
- ***Initiate a combination antiretroviral drug regimen, with regimen chosen based on resistance testing and prior antiretroviral therapy history, and avoid drugs with teratogenic potential (efavirenz in the first trimester of pregnancy) or with known adverse potential for the pregnant mother (e.g., combination stavudine/didanosine) (AII).***
- ***Women who do not show an appropriate virologic response to their antiretroviral regimens (see Monitoring of the Woman and Fetus During Pregnancy) require repeat antiretroviral drug resistance testing (AI), as well as consultation with a clinician experienced in HIV treatment, to guide changes in antiretroviral therapy.***

There are no data to guide the choice of antiretroviral regimens to be used in a subsequent pregnancy for women who previously received antiretroviral prophylaxis for prevention of perinatal HIV transmission. Although there is concern that time-limited use of antiretroviral drugs during pregnancy may lead to genotypic resistance, reduced efficacy of standard regimens, particularly those containing the dual NRTI backbone of zidovudine and lamivudine, in successive pregnancies has not been demonstrated. Given the lack of substantive data, it is reasonable to make preliminary decisions about antiretroviral regimens based on results of initial resistance testing. However, interpretation of resistance testing following discontinuation of antiretroviral drugs can be complex because the assay may not detect low-level drug-resistant viral variants. Thus, careful monitoring of virologic response to the chosen antiretroviral regimen is important. Decisions to alter therapy based on lack of virologic response should be guided by repeat resistance testing.

Some women may have received antiretroviral treatment for their own health in the past, having discontinued the drugs for a variety of reasons and for variable lengths of time prior to pregnancy. Appropriate choice of antiretroviral drugs will vary according to the history of antiretroviral use, the indication for stopping therapy, and the results of past and current resistance testing. For example, women with a history of prior antiretroviral therapy associated with successful suppression of viral load who then stopped all drugs simultaneously (or staggered discontinuation if NNRTI based) and who have no evidence of resistance may be able to restart the same regimen. Alternatively, selection of an appropriate antiretroviral regimen for women with advanced HIV disease, a history of extensive prior antiretroviral therapy, or history of significant toxicity to antiretroviral drugs in the past may be challenging even for health care providers experienced in HIV care. In addition to obtaining genotypic resistance testing as described above, it is recommended that specialists in the treatment of HIV infection be consulted about the choice of antiretroviral therapy in such cases.

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Table 4. Preclinical and Clinical Data Relevant to the Use of Antiretrovirals in Pregnancy (See *Supplement: Safety and Toxicity of Individual Antiretroviral Agents in Pregnancy* for more detail on drugs.)

Antiretroviral Generic name (Abbreviation)/ Trade name	FDA Pregnancy Category *	Placental Passage Newborn: Mother Drug Ratio	Long-term Animal Carcinogenicity Studies	Animal Teratogenicity Studies
Nucleoside and nucleotide analogue reverse transcriptase inhibitors				
Abacavir (ABC)/ Ziagen	C	Yes (rats)	Positive (malignant and non-malignant tumors of liver and thyroid in female rats and preputial and clitoral glands in mice and rats at 6–32x human exposure)	Positive (rodent anasarca and skeletal malformations at 1,000 mg/kg [35x human exposure] during organogenesis; not seen at 8.5x human exposure in rabbits)
Didanosine (ddI)/ Videx	B	Yes (humans) 0.5	Negative (no tumors in lifetime rodent study at 0.7–3x maximum human exposure)	Negative (at 12x and 14.2x human exposure in rabbits and rats, respectively)
Emtricitabine (FTC)/ Emtriva	B	Yes (mice and rabbits) 0.4–0.5	Negative (no tumors in lifetime rodent study at 26–31x human exposure)	Negative (at 60x, 60x, and 120x human exposure in rats, mice, and rabbits, respectively)
Lamivudine (3TC)/ Epivir	C	Yes (humans) ~1.0	Negative (no tumors in lifetime rodent study at 10–58x human exposure)	Negative (at 35x human exposure in rats and rabbits; however, embryolethality seen in rabbits at 1x human exposure)
Stavudine (d4T)/ Zerit	C	Yes (rhesus monkeys) 0.76	Positive (in mice and rats at very high dose exposure; liver and bladder tumors [rats only] at 250x and 732x human exposure in mice and rats, respectively)	Negative (at 399x [rats] and 183x [rabbits] human exposure, although sternal bone ossification decreased and rat neonatal mortality increased at 399x human exposure in rats)
Tenofovir DF (TDF)/ Viread	B	Yes (humans) 0.95–0.99	Positive (hepatic adenomas in female mice only at 16x human exposure)	Negative (at 14x and 19x human exposure in rats and rabbits, respectively)
Zidovudine (AZT, ZDV)/ Retrovir	C	Yes (humans) 0.85	Positive (nonmetastasizing vaginal epithelial tumors at 3x and 24x human exposure in mice and rats, respectively)	Positive (increased fetal malformations associated with maternal toxicity at 300x human exposure in rats. Increased fetal resorptions at 66–226x and 12–87x human exposure in rats and rabbits, respectively, with no developmental abnormalities)
Non-nucleoside reverse transcriptase inhibitors				
Efavirenz (EFV)/ Sustiva	D	Yes (cynomolgus monkeys, rats, rabbits) ~1.0	Positive (hepatocellular adenomas and carcinomas and pulmonary alveolar/bronchiolar adenomas in female mice at 1.7x human exposure; no increases in tumors in rats at 0.2x human exposure)	Positive (anencephaly, anophthalmia, microophthalmia, and cleft palate in cynomolgus monkey at exposures comparable to human exposure; no reproductive toxicities in pregnant rabbits at 0.5–1x human exposure)

Antiretroviral Generic name (Abbreviation)/ Trade name	FDA Pregnancy Category *	Placental Passage Newborn: Mother Drug Ratio	Long-term Animal Carcinogenicity Studies	Animal Teratogenicity Studies
Non-nucleoside reverse transcriptase inhibitors (cont)				
Etravirine (ETR)/ Intelence	B	Unknown	Positive (hepatocellular adenomas and carcinomas in female mice at 0.6x human exposure; no findings in rats at 0.2–0.7x human exposure)	Negative (in rats and rabbits at exposures comparable to human exposures)
Nevirapine (NVP)/ Viramune	B	Yes (humans) ~1.0	Positive (hepatocellular adenomas and carcinomas in mice and rats at less than human exposure)	Negative (in rats and rabbits at 1–1.5x human exposure; however, decreased fetal body weight in rats at 1.5x human exposure)
Protease inhibitors				
Atazanavir (ATV)/ Reyataz	B	Minimal/variable (humans)	Positive (benign hepatocellular adenomas in female mice at 7.2x human exposure)	Negative (at 2x and 1x human exposure in rats and rabbits, respectively)
Darunavir (DRV)/ Prezista	C	Unknown	Positive (hepatic adenomas, carcinomas [male mice], thyroid neoplasms [rats only] at 0.1–0.3x and 0.7–1x human exposure in mice and rats, respectively)	Negative (at 0.5x and 0.05x human exposure in rats/mice and rabbits, respectively)
Fosamprenavir (f-APV)/ Lexiva)	C	Unknown	Positive (hepatic adenomas and carcinomas [mice and rats]; thyroid adenomas, interstitial cell hyperplasia, and uterine endometrial adenocarcinoma [rats only] at 0.1–0.7x and 0.3–1.4x human exposure in mice and rats, respectively	Negative (at 0.8x and 2x human exposure in rabbits and rats respectively; increased incidence of abortions in rabbits at 0.8x human exposure)
Indinavir (IDV)/ Crixivan	C	Minimal (humans)	Positive (thyroid adenomas in male rats at 1.3x human exposure)	Negative (however supernumerary ribs in rats at exposures less than or slightly greater than human exposure)
Lopinavir + Ritonavir (LPV/r)/ Kaletra)	C	Yes (humans) 0.20±0.13	Positive (hepatic adenomas and carcinomas at 1.6–2.2x and 0.5x human exposure in mice and rats, respectively)	Positive (no effects in rabbits and dogs at ~1x human exposure; decreased fetal viability and body weight, delayed skeletal ossification and increase in skeletal variations in rats at maternally toxic doses [at 0.7x and 1.8x human exposure for lopinavir and ritonavir, respectively])
Nelfinavir (NFV)/ Viracept	B	Minimal/variable (humans)	Positive (thyroid follicular adenomas and carcinomas at 1–3x human exposure in rats)	Negative (in rats at human exposure and in rabbits at significantly lower than human exposure)

Antiretroviral Generic name (Abbreviation)/ Trade name	FDA Pregnancy Category *	Placental passage Newborn: Mother Drug Ratio	Long-term Animal Carcinogenicity Studies	Animal Teratogenicity Studies
Protease inhibitors (cont)				
Ritonavir (RTV)/ Norvir	B	Minimal (humans)	Positive (hepatic adenomas and carcinomas in male mice at 0.3x human exposure)	Positive (early resorptions, decreased fetal body weight, ossification delays, and developmental variations in rats at maternally toxic dose [~0.3x human exposure]; cryptorchidism in rats at 0.22x human exposure)
Saquinavir (SQV) Invirase	B	Minimal (humans)	Negative (at 0.29x and 0.65x human exposure [coadministration with ritonavir] in rats and mice, respectively)	Negative (at 0.29x and 0.21x human exposure [coadministration with ritonavir] in rats and rabbits, respectively)
Tipranavir (TPV)/ Aptivus	C	Unknown	Positive (hepatic adenomas and carcinomas in mice at less than human exposure; thyroid follicular cell adenoma in female rats at exposures comparable to human exposure)	Negative (decreased ossification and pup weights in rats at 0.8x human exposure)
Entry inhibitors				
Enfuvirtide (T-20)/ Fuzeon	B	None (based on very limited human data)	Not conducted	Negative
Maraviroc (MVC)/ Selzentry	B	Unknown	Negative (in transgenic mice and rats at 11x human exposure)	Negative (at 20x and 5x human exposure in rats and rabbits, respectively)
Integrase inhibitors				
Raltegravir (RAL)/ Isentress	C	Yes (rats, rabbits) † Rats: 1.5–2.5 Rabbits: 0.02	In progress	Negative (however, supernumerary ribs in rats at 3x human exposure)

* Food and Drug Administration Pregnancy Categories:
A - Adequate and well-controlled studies of pregnant women fail to demonstrate a risk to the fetus during the first trimester of pregnancy (and no evidence exists of risk during later trimesters).
B - Animal reproduction studies fail to demonstrate a risk to the fetus, and adequate but well-controlled studies of pregnant women have not been conducted.
C - Safety in human pregnancy has not been determined; animal studies are either positive for fetal risk or have not been conducted, and the drug should not be used unless the potential benefit outweighs the potential risk to the fetus.
D - Positive evidence of human fetal risk that is based on adverse reaction data from investigational or marketing experiences, but the potential benefits from the use of the drug among pregnant women might be acceptable despite its potential risks.
X - Studies among animals or reports of adverse reactions have indicated that the risk associated with the use of the drug for pregnant women clearly outweighs any possible benefit.

† Values obtained from fetal (not newborn) blood samples. See text under "Placental and breast milk passage" in section on Raltegravir (Isentress) in ***Supplement: Safety and Toxicity of Individual Antiretroviral Agents in Pregnancy***.

Table 5. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy

(See also "Supplement: Safety and Toxicity of Individual Antiretroviral Drugs in Pregnancy" for additional toxicity data and "Guidelines for the Use of Antiretroviral Agents in HIV-1-infected Adults and Adolescents" for detailed guidelines regarding treatment options.)

Antiretroviral Drug	Pharmacokinetics in Pregnancy	Concerns in Pregnancy	Recommendations for Use in Pregnancy
NRTIs/ NtRTIs		See text for discussion of potential maternal and infant mitochondrial toxicity.	NRTIs are recommended for use as part of combination regimens, usually including two NRTIs with either an NNRTI or one or more PIs. Use of single or dual NRTIs alone is not recommended for treatment of HIV infection. (Zidovudine alone may be considered for prophylaxis of perinatal transmission in pregnant women with HIV RNA <1,000 copies/mL.)
Recommended Agents			
Lamivudine*	Pharmacokinetics not significantly altered in pregnancy; no change in dose indicated *[1]*.	No evidence of human teratogenicity (can rule out 1.5-fold increase in overall birth defects) *[2]*. Well-tolerated, short-term safety demonstrated for mother and infant. If hepatitis B coinfected, possible hepatitis B flare if drug stopped postpartum (see **Special Considerations: Hepatitis B Virus Coinfection**).	Because of extensive experience with lamivudine in pregnancy in combination with zidovudine, lamivudine plus zidovudine is the recommended dual NRTI backbone for pregnant women.
Zidovudine*	Pharmacokinetics not significantly altered in pregnancy; no change in dose indicated *[3]*.	No evidence of human teratogenicity (can rule out 1.5-fold increase in overall birth defects) *[2]*. Well-tolerated, short-term safety demonstrated for mother and infant.	Preferred NRTI for use in combination antiretroviral regimens in pregnancy based on efficacy studies and extensive experience. Zidovudine should be included in the antenatal antiretroviral regimen unless there is severe toxicity, stavudine use, documented resistance, or the woman is already on a fully suppressive regimen.
Alternate Agents			
Abacavir*	Pharmacokinetics not significantly altered in pregnancy; no change in dose indicated.	No evidence of human teratogenicity (can rule out 2-fold increase in overall birth defects) *[2]*. Hypersensitivity reactions occur in ~5%–8% of nonpregnant persons; fatal reactions occur in a much smaller percentage of persons and are usually associated with rechallenge. Rate of hypersensitivity reactions in pregnancy is unknown. Testing for HLA-B*5701 identifies patients at risk of reactions *[4-5]* and should be done and documented as negative before starting abacavir. Patient should be educated regarding symptoms of hypersensitivity reaction.	Alternate NRTI for dual nucleoside backbone of combination regimens. See footnote regarding use in triple NRTI regimen. #
Didanosine	Pharmacokinetics not significantly altered in pregnancy; no change in dose indicated *[6]*.	Cases of lactic acidosis, some fatal, have been reported in pregnant women receiving didanosine and stavudine together *[7-8]*.	Alternate NRTI for dual nucleoside backbone of combination regimens. Didanosine should be used with stavudine only if no other alternatives are available.

Antiretroviral Drug	Pharmacokinetics in Pregnancy	Concerns in Pregnancy	Recommendations for Use in Pregnancy
Alternate Agents (continued)			
Emtricitabine†	Pharmacokinetic study shows slightly lower levels in third trimester compared to postpartum *[9]*. No clear need to increase dose.	No evidence of human teratogenicity (can rule out 2-fold increase in overall birth defects) *[2]*.	Alternate NRTI for dual nucleoside backbone of combination regimens.
Stavudine	Pharmacokinetics not significantly altered in pregnancy; no change in dose indicated *[10]*.	No evidence of human teratogenicity (can rule out 2-fold increase in overall birth defects) *[2]*. Cases of lactic acidosis, some fatal, have been reported in pregnant women receiving didanosine and stavudine together *[7-8]*.	Alternate NRTI for dual nucleoside backbone of combination regimens. Stavudine should be used with didanosine only if no other alternatives are available. Do not use with zidovudine due to potential for antagonism.
Use in Special Circumstances			
Tenofovir†	Limited studies in human pregnancy; data indicate AUC lower in third trimester than postpartum but trough levels similar.	No evidence of human teratogenicity (can rule out 2-fold increase in overall birth defects) *[2]*. Studies in monkeys at doses approximately 2-fold higher than dosage for human therapeutic use show decreased fetal growth and reduction in fetal bone porosity within 2 months of starting maternal therapy *[11]*. Clinical studies in humans (particularly children) show bone demineralization with chronic use; clinical significance unknown *[12-13]*. Significant placental passage in humans (cord:maternal blood ratio 0.6–0.99). If hepatitis B coinfected, possible hepatitis B flare if drug stopped postpartum (see **Special Considerations: Hepatitis B Virus Coinfection)**.	Because of limited data on use in human pregnancy and concern regarding potential fetal bone effects, tenofovir should be used as a component of a maternal combination regimen only after careful consideration of other alternatives. Because of potential for renal toxicity, renal function should be monitored.
NNRTIs		Hypersensitivity reactions, including hepatic toxicity, and rash more common in women; unclear if increased in pregnancy.	NNRTIs are recommended for use in combination regimens with 2 NRTI drugs.
Recommended Agents			
Nevirapine	Pharmacokinetics not significantly altered in pregnancy; no change in dose indicated *[14-15]*.	No evidence of human teratogenicity (can rule out 2-fold increase in overall birth defects) *[2]*. Increased risk of symptomatic, often rash-associated, and potentially fatal liver toxicity among women with CD4 counts >250/mm^3 when first initiating therapy *[16-17]*; unclear if pregnancy increases risk.	Nevirapine should be initiated in pregnant women with CD4 counts >250 cells/mm^3 only if benefit clearly outweighs risk, due to the increased risk of potentially life-threatening hepatotoxicity in women with high CD4 counts. Women who enter pregnancy on nevirapine regimens and are tolerating them well may continue therapy, regardless of CD4 count.

Antiretroviral Drug	Pharmacokinetics in Pregnancy	Concerns in Pregnancy	Recommendations for Use in Pregnancy
Use in Special Circumstances			
Efavirenz†	Small study in 13 breastfeeding women in Rwanda of 600 mg once daily; postpartum peak levels during lactation were 61% higher than previously reported in HIV-infected nonpregnant individuals at that dose *[18]*.	FDA Pregnancy Class D; significant malformations (anencephaly, anophthalmia, cleft palate) were observed in 3 (15%) of 20 infants born to cynomolgus monkeys receiving efavirenz during the first trimester at a dose giving plasma levels comparable to systemic human therapeutic exposure. There are 6 retrospective case reports and 1 prospective case report of neural tube defects in humans with first-trimester exposure *[2, 19-20]*; relative risk unclear.	Use of efavirenz should be avoided in the first trimester. Use after the first trimester can be considered if, after consideration of other alternatives, this is the best choice for a specific woman. If efavirenz is to be continued postpartum, adequate contraception must be assured. Women of childbearing potential must be counseled regarding the teratogenic potential of efavirenz and avoidance of pregnancy while on the drug. Because of the known failure rates even with contraception, alternate antiretroviral regimens should be strongly considered in women of childbearing potential.
Insufficient Data to Recommend Use			
Etravirine	No pharmacokinetic studies in human pregnancy.	No experience in human pregnancy.	Safety and pharmacokinetics in pregnancy data are insufficient to recommend use during pregnancy.
Protease Inhibitors (PIs)		Hyperglycemia, new onset or exacerbation of diabetes mellitus, and diabetic ketoacidosis reported with PI use; unclear if pregnancy increases risk. Conflicting data regarding preterm delivery in women receiving PIs (see text).	PIs are recommended for use in combination regimens with 2 NRTI drugs.
Recommended Agents			
Lopinavir/ ritonavir	Pharmacokinetic studies of the new lopinavir/ ritonavir tablet formulation are under way, but data are not yet available.	No evidence of human teratogenicity (can rule out 2-fold increase in overall birth defects) *[2]*. Well-tolerated, short-term safety demonstrated in Phase I/II studies.	Pharmacokinetic studies of the new tablet formulation are under way but are not yet conclusive as to the optimal dose in pregnancy. Some experts would administer standard dosing (2 tablets twice daily) throughout pregnancy and monitor virologic response and lopinavir drug levels, if available. Other experts, extrapolating from the capsule formulation pharmacokinetic data, would increase the dose of the tablet formulation during the third trimester (from 2 tablets to 3 tablets twice daily), returning to standard dosing postpartum. Once-daily lopinavir/ritonavir dosing is not recommended during pregnancy because there are no data to address whether drug levels are adequate with such administration.

Antiretroviral Drug	Pharmacokinetics in Pregnancy	Concerns in Pregnancy	Recommendations for Use in Pregnancy
Alternate Agents			
Atazanavir (recommended to be combined with low-dose ritonavir boosting)	Two of three intensive pharmacokinetic studies of atazanavir with ritonavir boosting during pregnancy suggest that standard dosing results in decreased plasma concentrations compared to nonpregnant adults *[21-23]*. Atazanavir concentrations further reduced ~25% with concomitant tenofovir use *[23]*.	No evidence of human teratogenicity (can rule out 2-fold increase in overall birth defects) *[2]*. Transplacental passage is low, with cord blood concentration averaging 10%–16% of the maternal delivery atazanavir concentration *[21, 23]*. Theoretical concern re: increased indirect bilirubin levels exacerbating physiologic hyperbilirubinemia in the neonate not observed in clinical trials to date *[21-24]*.	Alternative PI for use in combination regimens in pregnancy. Should give as low-dose ritonavir-boosted regimen, may use once-daily dosing. In treatment-naïve patients unable to tolerate ritonavir, 400 mg once-daily dosing without ritonavir boosting may be considered, although there are no data describing atazanavir concentrations or efficacy under these circumstances. If coadministered with tenofovir, atazanavir must be given with low-dose ritonavir boosting.
Indinavir (combined with low-dose ritonavir boosting)	Two studies including 18 women receiving indinavir 800 mg three times daily showed markedly lower levels during pregnancy compared to postpartum, although suppression of HIV RNA was seen *[25-26]*. In a study of ritonavir-boosted indinavir (400 mg indinavir/100 mg ritonavir twice daily), 82% of women met the target trough level *[27]*.	No evidence of human teratogenicity (can rule out 2-fold increase in overall birth defects) *[2]*. Theoretical concern re: increased indirect bilirubin levels, which may exacerbate physiologic hyperbilirubinemia in the neonate, but minimal placental passage. Use of unboosted indinavir during pregnancy is not recommended.	Alternate PI for use in combination regimens in pregnancy. Must give as low-dose ritonavir-boosted regimen.
Nelfinavir	Adequate drug levels are achieved in pregnant women with nelfinavir 1,250 mg given twice daily, although levels are variable in late pregnancy *[28-30]*. In a study of pregnant women in their second and third trimester dosed at 1,250 mg given twice daily, women in the third trimester had lower concentration of nelfinavir than women in the second trimester *[30]*. In a study of the new 625-mg tablet formulation dosed at 1,250 mg twice daily, lower AUC and peak levels were observed during the third trimester of pregnancy than postpartum *[31]*.	No evidence of human teratogenicity (can rule out 2-fold increase in overall birth defects) *[2]*. Well-tolerated, short-term safety demonstrated for mother and infant.	Given pharmacokinetic data and extensive experience with use in pregnancy, nelfinavir is an alternative PI for combination regimens in pregnant women receiving combination antiretroviral drugs only for perinatal prophylaxis. In clinical trials of initial therapy in nonpregnant adults, nelfinavir-based regimens had a lower rate of viral response compared to lopinavir-ritonavir or efavirenz-based regimens but similar viral response to atazanavir- or nevirapine-based regimens.

Antiretroviral Drug	Pharmacokinetics in Pregnancy	Concerns in Pregnancy	Recommendations for Use in Pregnancy
Alternate Agents (continued)			
Ritonavir	Phase I/II study in pregnancy showed lower levels during pregnancy compared to postpartum *[2, 32]*.	Limited experience at full dose in human pregnancy; has been used as low-dose ritonavir boosting with other PIs.	Given low levels in pregnant women when used alone, recommended for use in combination with second PI as low-dose ritonavir "boost" to increase levels of second PI.
Saquinavir HGC (combined with low-dose ritonavir boosting)	Limited pharmacokinetic data on saquinavir HGC and the new 500-mg tablet formulation suggest that 1,000 mg saquinavir HGC/100 mg ritonavir given twice daily achieves adequate saquinavir drug levels in pregnant women *[33]*.	Well-tolerated, short-term safety demonstrated for mother and infant for saquinavir in combination with low-dose ritonavir.	There are only limited pharmacokinetic data on saquinavir HGC and the new tablet formulation in pregnancy. Ritonavir-boosted saquinavir HGC or saquinavir tablets are alternative PIs for combination regimens in pregnancy and are alternative initial antiretroviral recommendations for nonpregnant adults. Must give as low-dose ritonavir-boosted regimen.
Insufficient Data to Recommend Use			
Darunavir (combined with low-dose ritonavir boosting)	No pharmacokinetic studies in human pregnancy.	No experience in human pregnancy.	Safety and pharmacokinetics in pregnancy data are insufficient to recommend use during pregnancy. Must give as low-dose ritonavir-boosted regimen.
Fosamprenavir (recommended to be combined with low-dose ritonavir boosting)	No pharmacokinetic studies in human pregnancy.	Limited experience in human pregnancy.	Safety and pharmacokinetics in pregnancy data are insufficient to recommend use during pregnancy. Recommended to be given as low-dose ritonavir-boosted regimen.
Tipranavir (combined with low-dose ritonavir boosting)	No pharmacokinetic studies in human pregnancy.	No experience in human pregnancy.	Safety and pharmacokinetics in pregnancy data are insufficient to recommend use during pregnancy. Must give as low-dose ritonavir-boosted regimen.
Entry Inhibitors			
Insufficient Data to Recommend Use			
Enfuvirtide	No pharmacokinetic studies in human pregnancy.	Minimal data in human pregnancy *[34]*.	Safety and pharmacokinetics in pregnancy data are insufficient to recommend use during pregnancy.
Maraviroc	No pharmacokinetic studies in human pregnancy.	No experience in human pregnancy.	Safety and pharmacokinetics in pregnancy data are insufficient to recommend use during pregnancy.

Antiretroviral Drug	Pharmacokinetics in Pregnancy	Concerns in Pregnancy	Recommendations for Use in Pregnancy
Integrase Inhibitors			
Insufficient Data to Recommend Use			
Raltegravir	No pharmacokinetic studies in human pregnancy.	No experience in human pregnancy.	Safety and pharmacokinetics in pregnancy data are insufficient to recommend use during pregnancy.

Abbreviations: AUC: area under the curve; HGC: hard gel capsule; NRTI: nucleoside reverse transcriptase inhibitor; NtRTI: nucleotide reverse transcriptase inhibitor; NNRTI: non-nucleoside reverse transcriptase inhibitor; PI: protease inhibitor.

* Zidovudine and lamivudine are included as a fixed-dose combination in Combivir; zidovudine, lamivudine, and abacavir are included as a fixed-dose combination in Trizivir; lamivudine and abacavir are included as a fixed-dose combination in Epzicom.

† Emtricitabine and tenofovir are included as a fixed-dose combination in Truvada; emtricitabine, tenofovir, and efavirenz are included as a fixed-dose combination in Atripla.

\# Triple NRTI regimens including abacavir have been less potent virologically compared to PI-based combination antiretroviral drug regimens. Triple NRTI regimens should be used only when an NNRTI- or PI-based combination regimen cannot be used (e.g., due to significant drug interactions).

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Table 6. Clinical Scenario Summary Recommendations for Antiretroviral Drug Use by Pregnant HIV-Infected Women and Prevention of Perinatal Transmission of HIV-1 in the United States

Clinical Scenario	Recommendations
Nonpregnant HIV-infected woman of childbearing potential who has indications for initiating antiretroviral therapy	• Initiate combination antiretroviral drug therapy as per adult treatment guidelines. • Avoid drugs with teratogenic potential (e.g., efavirenz) if the woman is trying to conceive or is not using adequate contraception. Exclude pregnancy before starting treatment with efavirenz.
HIV-infected woman on combination antiretroviral drug therapy who becomes pregnant	**Woman:** • In general, if woman requires treatment, antiretroviral drugs should not be stopped during the first trimester or during pregnancy. • Continue current combination antiretroviral therapy regimen if successfully suppressing viremia; however, avoid use of efavirenz or other potentially teratogenic drugs in the first trimester and drugs with known adverse potential for mother (e.g., combination stavudine/didanosine) throughout the pregnancy. • Perform HIV antiretroviral drug resistance testing if the woman has detectable viremia on therapy. • Continue combination antiretroviral therapy regimen during intrapartum period (zidovudine given as continuous infusion[1] during labor while other antiretroviral agents are continued orally) and postpartum. • Schedule cesarean delivery at 38 weeks gestation if plasma HIV RNA remains >1,000 copies/mL near the time of delivery. **Infant:** • Start zidovudine as soon as possible after birth and administer for 6 weeks.[2]
HIV-infected pregnant woman who is antiretroviral naïve and has indications for antiretroviral therapy	**Woman:** • Perform HIV antiretroviral drug resistance testing prior to initiating combination antiretroviral drug therapy and repeat after initiating therapy if viral suppression is suboptimal. • Initiate combination antiretroviral regimen. - Avoid use of efavirenz or other potentially teratogenic drugs in the first trimester and drugs with known adverse potential for mother (e.g., combination stavudine/didanosine). - Use zidovudine as a component of the antiretroviral regimen when feasible. - Use nevirapine as a component of the antiretroviral regimen only if the woman has CD4 count ≤250 cells/mm^3. If the woman has CD4 count >250 cells/mm^3, use nevirapine as a component of therapy only if the benefit clearly outweighs the risk due to an increased risk of severe hepatic toxicity. • If woman requires immediate initiation of therapy for her own health, initiate treatment as soon as possible, including in the first trimester. • Continue combination antiretroviral therapy regimen during intrapartum period (zidovudine given as continuous infusion[1] during labor while other antiretroviral agents are continued orally) and postpartum. • Schedule cesarean delivery at 38 weeks gestation if plasma HIV RNA remains >1,000 copies/mL near the time of delivery. **Infant:** • Start zidovudine as soon as possible after birth and administer for 6 weeks.[2]

Clinical Scenario	Recommendations
HIV-infected pregnant woman who is antiretroviral naïve and does not require treatment for her own health	**Woman:** • Perform HIV antiretroviral drug resistance testing prior to initiating combination antiretroviral drug therapy and repeat after initiation of therapy if viral suppression is suboptimal. • Prescribe a combination antiretroviral drug prophylaxis regimen (i.e., at least 3 drugs) for prophylaxis of perinatal transmission. - Consider delaying initiation of antiretroviral prophylaxis until after first trimester is completed. - Avoid use of efavirenz or other potentially teratogenic drugs in the first trimester and drugs with known adverse potential for mother (e.g., combination stavudine/didanosine). - Use zidovudine as a component of the antiretroviral regimen when feasible. - If the woman has CD4 count >250 cells/mm^3 use nevirapine as a component of therapy only if the benefit clearly outweighs the risk due to an increased risk of severe hepatic toxicity. • Although use of zidovudine prophylaxis alone is controversial, consider if woman has plasma HIV RNA level <1,000 copies/mL on no therapy. • Continue antiretroviral prophylaxis regimen during intrapartum period (zidovudine given as continuous infusion[1] during labor while other antiretroviral agents are continued orally). • Evaluate need for continuing the combination regimen postpartum; discontinue the combination regimen unless the woman has indications for continued therapy. If regimen includes drug with long half-life like NNRTI, consider stopping NRTIs at least 7 days after stopping NNRTI. (Only limited data exist on this; see **Stopping Antiretroviral Therapy** and **Prevention of Antiretroviral Drug Resistance**.) • Schedule cesarean delivery at 38 weeks gestation if plasma HIV RNA remains >1,000 copies/mL near the time of delivery. **Infant**: • Start zidovudine as soon as possible after birth and administer for 6 weeks.[2]
HIV-infected pregnant woman who is antiretroviral experienced but not currently receiving antiretroviral drugs	**Woman:** • Obtain full antiretroviral treatment history, including prior resistance testing, and evaluate need for antiretroviral treatment for maternal health. • Perform HIV antiretroviral drug resistance testing prior to initiating repeat antiretroviral prophylaxis or therapy and repeat after initiating combination antiretroviral regimen if suboptimal viral suppression. • Initiate a combination antiretroviral regimen (e.g., at least 3 drugs), with regimen chosen based on resistance testing and prior therapy history. - Avoid use of efavirenz or other potentially teratogenic drugs in the first trimester and drugs with known adverse potential for the mother (e.g., combination stavudine/didanosine). - Use zidovudine as a component of the antiretroviral regimen when feasible. - If woman has CD4 count >250 cells/mm^3, use nevirapine as a component of therapy only if the benefit clearly outweighs the risk due to an increased risk of severe hepatic toxicity. • Continue the combination regimen during intrapartum period (zidovudine given as continuous infusion[1] during labor while other antiretroviral agents are continued orally). • Evaluate need for continuing the combination regimen postpartum; discontinue the combination regimen unless the woman has indications for continued therapy. If regimen includes drug with long half-life like NNRTI, consider stopping NRTIs at least 7 days after stopping NNRTI. (Limited data exist on this; see **Stopping Antiretroviral Therapy** and **Prevention of Antiretroviral Drug Resistance**.)

Clinical Scenario	Recommendations
	• Schedule cesarean delivery at 38 weeks gestation if plasma HIV RNA remains >1,000 copies/mL near the time of delivery. **Infant**: • Start zidovudine as soon as possible after birth and administer for 6 weeks.[2]
HIV-infected woman who has received no antiretroviral therapy prior to labor	Zidovudine **Woman:** Give zidovudine as continuous infusion[1] during labor. **Infant:** Start zidovudine as soon as possible after birth and administer for 6 weeks.[2] ***OR*** Combination Zidovudine + Single-dose Nevirapine **Woman:** Give zidovudine as continuous infusion[1] during labor, plus single-dose nevirapine [3] at onset of labor. Consider adding lamivudine during labor and maternal zidovudine/lamivudine for at least 7 days postpartum, which may reduce development of nevirapine resistance. **Infant:** Give single-dose nevirapine[3] plus zidovudine for 6 weeks. ***OR*** **Woman:** Give zidovudine as continuous infusion[1] during labor. **Infant:** Although some clinicians may choose to use zidovudine in combination with additional drugs in the infant, appropriate dosing for neonates is incompletely defined and the additional efficacy of this approach in reducing transmission is not known. Consider consultation with a pediatric HIV specialist. • Evaluate need for initiation of maternal therapy postpartum.
Infant born to HIV-infected woman who has received no antiretroviral therapy prior to or during labor	• Start zidovudine as soon as possible after birth and administer for 6 weeks.[2] ***OR*** • Although some clinicians may choose to use zidovudine in combination with additional drugs, appropriate dosing for neonates is incompletely defined and the additional efficacy of this approach in reducing transmission is not known. Consider consultation with a pediatric HIV specialist. • Evaluate need for initiation of maternal therapy postpartum.

[1] Zidovudine continuous infusion: 2 mg/kg zidovudine intravenously over 1 hour, followed by continuous infusion of 1 mg/kg/hour until delivery.

[2] Zidovudine dosing for infants <35 weeks gestation at birth is 1.5 mg/kg/dose intravenously or 2.0 mg/kg/dose orally, every 12 hours, advancing to every 8 hours at 2 weeks of age if ≥30 weeks gestation at birth or at 4 weeks of age if <30 weeks gestation at birth.

[3] Single-dose nevirapine: Mother: 200 mg given once orally at onset of labor; Infant: 2 mg/kg body weight given once orally at 2–3 days of age if mother received intrapartum single-dose nevirapine or given at birth if mother did not receive intrapartum single-dose nevirapine.

Hepatitis B Virus Coinfection

Panel's Recommendations:

- ***Screening for hepatitis B virus (HBV) infection is recommended for all HIV-infected pregnant women who have not been screened during the current pregnancy (AII).***
- ***Pregnant women who screen negative for hepatitis B should receive the HBV vaccine series (AII).***
- ***Pregnant women with HBV infection should be screened for hepatitis A virus (HAV) and those who screen negative should receive the HAV vaccine series (AII).***
- ***Interferon-alpha and pegylated interferon-alpha are not recommended during pregnancy (AIII).***
- ***Because the optimal management for pregnant and postpartum women with HIV/HBV coinfection is not well defined, consultation with an expert in HIV and HBV is strongly recommended (AIII).***
- ***Decisions about the choice of antiretroviral regimen during pregnancy for HIV/HBV-coinfected women should take into account indications for HIV therapy as determined by maternal CD4 cell count and HIV disease status, HBV levels and indications for HBV therapy, gestational age when starting the antiretroviral regimen, and patient preference (AIII).***
- ***The determination of optimal antepartum antiretroviral regimen for an HIV/HBV-coinfected woman depends on whether she requires anti-HIV treatment for her own health, anti-HBV treatment, both, or neither.***
    - ***For coinfected women with indications for antiretroviral therapy for their own health and who are expected to continue drugs postpartum and/or who require treatment for HBV infection:***
        - ***A three-drug combination antepartum antiretroviral regimen including two agents with anti-HBV activity (e.g., tenofovir plus either lamivudine or emtricitabine) should be used and continued postpartum (BII).***
    - ***For coinfected women who receive antiretroviral drugs during pregnancy solely as prophylaxis for prevention of mother-to-child transmission of HIV, who are expected to discontinue antiretroviral prophylaxis after delivery, and who do not require treatment for HBV infection, the choice is more complex and can include:***
        - ***A three-drug combination antepartum antiretroviral regimen including two NRTI agents with anti-HBV activity (e.g., tenofovir plus either lamivudine or emtricitabine) and stopping prophylaxis after delivery (with monitoring for HBV flare) (BIII); or***
        - ***A three-drug combination antepartum antiretroviral regimen that includes only NRTI agents without anti-HBV activity (e.g., abacavir, didanosine, stavudine, or zidovudine) and stopping prophylaxis after delivery (BIII); or***
        - ***A three-drug combination antepartum antiretroviral regimen including lamivudine as the sole anti-HBV agent could be considered for women presenting late in pregnancy (e.g., after 28 weeks gestation) and stopping prophylaxis after delivery (with monitoring for HBV flare) (CIII).***
- ***Pregnant women with HBV/HIV coinfection receiving antiretroviral drugs should be counseled about signs and symptoms of liver toxicity, and liver transaminases should be assessed 2 weeks following initiation of antiretroviral therapy or prophylaxis and then at least monthly (BIII).***
- ***Infants born to women with hepatitis B infection should receive hepatitis B immune globulin (HBIG) and the first dose of the hepatitis B vaccine series within 12 hours of birth; the second and third doses of vaccine should be administered at 1 and 6 months of age, respectively (AI).***

For additional information on hepatitis B and HIV, see *Hepatitis B Virus Infection* (pages 75–84) in the "Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents, Recommendations from CDC, NIH, and the HIV Medicine Association (HIVMA) of the Infectious Diseases Society of America (IDSA)" at **http://www.cdc.gov/mmwr/pdf/rr/rr5804.pdf** *[1]*.

All HIV-infected pregnant women should be screened for hepatitis A, B, and C. The management of HBV/HIV coinfection in pregnancy is complex and consultation with an expert in HIV and HBV infection is strongly recommended. HIV-infected women who are found to have chronic hepatitis B on the basis of hepatitis B surface antigen for at least 6 months and who are hepatitis A IgG negative should receive the hepatitis A virus (HAV) vaccine series because of the added risk of acute hepatitis A in persons with chronic viral hepatitis.

HIV-infected women who are found to be hepatitis B surface antibody and hepatitis B surface antigen negative should receive the HBV vaccine series. Some patients test positive for anti-HBc alone, which might signify a false-positive result; exposure in the past with subsequent loss of anti-HBs; or "occult" HBV infection, which can be confirmed by detection of HBV DNA *[2-3]*. The clinical significance of isolated anti-HBc is unknown *[4-5]*. Some specialists recommend that HIV-infected persons with anti-HBc alone should be tested for HBV DNA before vaccination for HBV or before initiating antiretroviral drug treatment or prophylaxis because of the risk of reactivation of HBV and the occurrence of immune reconstitution inflammatory syndrome (IRIS) *[1]*. There are limited data regarding the optimal treatment of HIV-infected pregnant women with chronic HBV coinfection (i.e., hepatitis B surface antigen positive for >6 months). There are no definitive studies on the safety of antiviral therapy for hepatitis B infection during pregnancy and breastfeeding; interferon and peg-interferon are not recommended during pregnancy.

Current treatment guidelines for HBV/HIV-coinfected nonpregnant adults who require treatment of their HIV infection recommend the NRTI combination of tenofovir plus emtricitabine or tenofovir plus lamivudine as the dual NRTI backbone of an antiretroviral regimen, regardless of the need for concomitant HBV treatment *[6]*.Tenofovir, lamivudine, and emtricitabine all show activity against HBV. Because of the risk of development of HBV-resistant mutants, use of two agents active against HBV (tenofovir plus lamivudine or emtricitabine) is recommended as the dual NRTI backbone when antiretroviral treatment is required.

Lamivudine is a recommended NRTI and emtricitabine is an alternative NRTI for use in pregnancy. There are only limited data on the use of tenofovir during pregnancy. Tenofovir is not teratogenic in animals but reversible bone changes at high doses were seen in multiple animal species. Although tenofovir is not generally recommended in pregnancy as a first-line agent for antiretroviral regimens being used solely for prophylaxis of mother-to-child transmission of HIV, HBV/HIV coinfection in pregnancy may be a special circumstance where tenofovir may be more strongly considered (see **Table 5**). For pregnant women with HBV/HIV coinfection who require treatment of HIV disease for their own health or who require treatment of chronic HBV disease, the benefit of tenofovir outweighs potential risks, and tenofovir plus lamivudine or emtricitabine is recommended as the dual NRTI backbone of a three-drug therapeutic regimen. Although zidovudine should generally be a component of antiretroviral regimens in pregnancy, in HBV/HIV-coinfected women this may not be feasible.

A three-drug regimen including tenofovir plus lamivudine or emtricitabine is also recommended for HBV/HIV-coinfected pregnant women who do not require treatment of HIV but who do require treatment of their HBV disease. In nonpregnant coinfected patients who require treatment of HBV disease but not of HIV, pegylated interferon-alpha treatment is recommended. However, this drug is not recommended in pregnancy. Additionally, the use of tenofovir plus lamivudine or emtricitabine without a third antiretroviral drug should be avoided because of the rapid development of drug-resistant HIV mutations. Entecavir should not be used for treatment of HBV infection without concomitant combination treatment for HIV infection because recent data suggest that the M184V resistance mutation may emerge in HIV-infected patients receiving entecavir alone *[7]*. Entecavir is associated with skeletal anomalies in rats and rabbits but only at high, maternally toxic doses. Data on use of entecavir in human pregnancy are not available. Postpartum, the patient could stop the antiretroviral regimen and initiate HBV-specific therapy (e.g., pegylated interferon-alpha) to continue HBV treatment or continue the three-drug antiretroviral regimen.

There is controversy regarding the appropriate approach to therapy for pregnant women with HBV/HIV coinfection who do not require treatment of HIV or HBV disease, and therefore are receiving antiretroviral drugs solely for prevention of perinatal transmission of HIV and will discontinue therapy postpartum. Although there are only limited data about the safety of tenofovir in pregnancy, some experts recommend use of a three-drug regimen that includes the anti-HBV drug tenofovir plus lamivudine or emtricitabine as the dual NRTI backbone due to concern about HBV immune reconstitution inflammatory syndrome (IRIS) with initiation of therapy. Although concern about antiretroviral treatment-induced HBV IRIS should be less in this group of pregnant women because they do not require therapy for their own health and therefore do not have severe immunodeficiency (the greatest risk factor for development of IRIS following initiation of antiretroviral therapy), treating a potential HBV flare in the postpartum period after discontinuing HBV-active therapy may be associated with less risk than treating an immune-mediated flare during pregnancy. In addition, using drugs with anti-HBV activity during pregnancy will lower HBV levels and potentially decrease the risk of failure of hepatitis B immune globulin (HBIG) and hepatitis B vaccine to prevent perinatal transmission of HBV, which is increased among women with very high HBV DNA levels. If such an approach is followed, liver function should be carefully monitored postpartum following discontinuation of drugs; if severe flare-up of HBV disease occurs postpartum, initiation of anti-HBV-specific therapy such as pegylated interferon-alpha can be considered.

Alternatively, for women who require prophylaxis of perinatal HIV infection but do not require treatment for HBV infection, some experts choose to use an antiretroviral regimen without anti-HBV activity (e.g., use of a dual NRTI backbone that contains drugs other than tenofovir, lamivudine, or emtricitabine, such as zidovudine and didanosine, could be considered) to avoid the possibility of an HBV flare when treatment is discontinued postpartum. Another alternative used by some specialists for women who require prophylaxis of perinatal HIV infection but do not require treatment of HBV infection is a highly active antiretroviral regimen that includes lamivudine as the only antiretroviral agent with activity against HBV, especially if the regimen is started later in pregnancy because of late care or delayed HIV diagnosis. This option avoids the use of tenofovir during pregnancy because there are only limited data on safety, while still treating HBV; the risk of HBV development of resistance to lamivudine with short-term temporary exposure of less than 6 months is extremely low *[8]*.

An elevation in hepatic enzymes following initiation of antiretroviral therapy may occur in HBV/HIV-coinfected women due to an immune-mediated flare in HBV disease secondary to immune reconstitution with therapy, particularly in women with low CD4+ cell count at the time of initiation of therapy. HBV infection may also increase hepatotoxic risk of certain antiretroviral agents, specifically protease inhibitors and nevirapine. Pregnant women with HBV/HIV coinfection should be counseled about signs and symptoms of liver toxicity, and transaminases should be assessed 2 weeks following initiation of antiretroviral therapy or prophylaxis in women not already receiving drugs and then at least monthly. If hepatic toxicity occurs, substitution of a less hepatotoxic drug regimen may need to be considered or, if clinical symptoms or significant elevations of transaminases occur, drugs may need to be temporarily discontinued. It can be difficult to differentiate a flare in HBV disease due to immune reconstitution from drug toxicity, and consultation with an expert in HIV infection is recommended.

All infants born to HBV surface antigen positive mothers should receive hepatitis B immune globulin (HBIG) and the first dose of the hepatitis B vaccination series within 12 hours of birth. The second and third doses of vaccine should be administered at 1 and 6 months of age, respectively. This regimen is >95% effective in preventing HBV infection in these infants.

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Hepatitis C Virus Coinfection

Panel's Recommendations:

- ***Screening for hepatitis C virus (HCV) infection is recommended for all HIV-infected pregnant women who have not been screened during the current pregnancy (AIII).***
- ***Pegylated interferon-alpha is not recommended and ribavirin is contraindicated during pregnancy (AII).***
- ***Recommendations for antiretroviral drug use during pregnancy are the same for women who are coinfected with HCV as for those without HCV coinfection (BIII).***
- ***Pregnant women with HCV/HIV coinfection receiving antiretroviral drugs should be counseled about signs and symptoms of liver toxicity, and transaminases should be assessed 2 weeks following initiation of antiretroviral therapy or prophylaxis in women not already receiving drugs and then at least monthly (BIII).***
- ***Decisions concerning mode of delivery in HCV/HIV-coinfected pregnant women should be based on considerations related to HIV infection alone (see Intrapartum Care) (BIII).***
- ***Infants born to women with HCV/HIV coinfection should be evaluated for HCV infection (AIII) by HCV RNA testing between 2 and 6 months of age and/or HCV antibody testing after 15 months of age (CIII).***
- ***Because of the added risk of acute hepatitis A and B in persons with chronic viral hepatitis C, women who are found to have chronic HCV infection should be screened for hepatitis A and hepatitis B infections. If women with chronic hepatitis C are hepatitis A IgG negative, they should receive the hepatitis A virus (HAV) vaccine series, and if they are hepatitis B uninfected (e.g., hepatitis B surface Ag negative, hepatitis B core antibody negative, and hepatitis B surface antibody negative), they should receive the HBV vaccine series (AIII).***

For additional information on hepatitis C and HIV, see *Hepatitis C Virus Infection* (pages 84–91) of the "Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-infected Adults and Adolescents, Recommendations from CDC, NIH, and the HIV Medicine Association (HIVMA) of the Infectious Diseases Society of America (IDSA)" at **http://www.cdc.gov/mmwr/pdf/rr/rr5804.pdf** *[1]*.

HCV/HIV coinfection is not uncommon in HIV-infected women, particularly among women infected via parenteral drug use; among HIV-infected pregnant women, the HCV seroprevalence rate ranges from 17%–54% *[2]*. Screening for HCV infection using a sensitive immunoassay for HCV antibody is recommended for all HIV-infected individuals, including pregnant women. False-negative anti-HCV immunoassay results may occur among HIV-infected persons, particularly those with very low CD4 counts, but this is uncommon with the most sensitive immunoassays. If serologic test results are indeterminate or HCV infection is suspected due to elevated aminotransaminases or risk factors such as a history of intravenous drug use, testing for HCV RNA should be performed.

There are few data on the optimal management of HIV-infected pregnant women with HCV coinfection. There are no definitive studies on the safety of HCV antiviral therapy during pregnancy. Interferon and peg-interferon are not recommended for use in pregnancy, and ribavirin is contraindicated in pregnancy. Although interferons are not teratogenic, they are abortifacient at high doses in monkeys and should not be used in pregnant women because of the direct antigrowth and antiproliferative effects of these agents *[3]*. Ribavirin is labeled as FDA pregnancy category X because of its teratogenicity at low doses in multiple animal species; defects noted in animals include limb abnormalities, craniofacial defects, anencephaly, and anophthalmia. Pregnancy does not appear to influence the course of HCV infection and women with chronic viral hepatitis generally do quite well during pregnancy, providing that they have not progressed to decompensated cirrhosis *[4]*.

Because of the added risk of acute hepatitis A and B in persons with chronic viral hepatitis C, women who are found to have chronic HCV infection should be screened for hepatitis A and hepatitis B infections. If women with chronic HCV infection are hepatitis A IgG negative, they should receive the HAV vaccine series, and if they are hepatitis B uninfected (e.g., hepatitis B surface Ag negative, hepatitis B core antibody negative, and hepatitis B surface antibody negative), they should receive the HBV vaccine series.

Coinfection with HIV has been shown to increase significantly the risk of perinatal transmission of HCV, likely related to increase in HCV viremia and/or other HIV-related impact on HCV disease activity *[5]*. A European study of perinatal transmission of HCV found that use of effective combination antiretroviral therapy was associated with a strong trend for reduction in HCV transmission (OR 0.26, 95% CI, 0.07–1.01) *[6]*. However, although the median HCV viral load was lower among women treated with combination antiretroviral regimens compared to women on a single drug or receiving no treatment (656,101 copies/mL vs. 850,000 copies/mL, respectively), this difference was neither statistically nor clinically significant. Maternal HCV/HIV coinfection may also increase the risk of perinatal transmission of HIV *[7]*. Therefore, potent combination antiretroviral therapy with three drugs should be considered for all HCV/HIV-coinfected pregnant women, regardless of CD4 count or HIV viral load, with discontinuation of therapy postpartum in women who do not require therapy for their own health.

Similar to HBV infection, an elevation in hepatic enzymes following initiation of antiretroviral therapy may occur in HCV/HIV-coinfected women. This elevation in hepatic enzymes may be due to an immune-mediated flare in HCV disease secondary to immune reconstitution with therapy, particularly in women with low CD4 cell count at the time of initiation of therapy. Like HBV, HCV infection may increase hepatotoxic risk of certain antiretroviral agents, specifically protease inhibitors and nevirapine. Pregnant women with HCV/HIV coinfection should be counseled about signs and symptoms of liver toxicity, and transaminases should be assessed 2 weeks following initiation of antiretroviral therapy or prophylaxis in women not already receiving drugs and then at least monthly. If hepatic toxicity occurs, substitution of a less hepatotoxic drug regimen may need to be considered or, if clinical symptoms or significant elevations of transaminases occur, drugs may need to be temporarily discontinued. It can be difficult to differentiate a flare in HCV disease due to immune reconstitution from drug toxicity, and consultation with an expert in HIV infection is recommended.

Similar to HIV transmission, internal fetal monitoring and duration of membrane rupture greater than 6 hours may increase risk of HCV transmission; general recommendations for intrapartum management are unchanged from those for women with HIV infection alone (see **Intrapartum Care**). Data are inconclusive regarding the role of scheduled cesarean delivery in reducing the risk of HCV transmission in the setting of HIV infection. Currently, there is no evidence from randomized controlled trials upon which to base any practice recommendations regarding scheduled cesarean delivery versus vaginal delivery for preventing mother-to-infant transmission of HCV *[8]*. In two observational studies from the European Hepatitis C Virus Network, the first study reported that scheduled cesarean delivery was protective against HCV transmission in HIV-coinfected women, but the second study found no benefit to scheduled cesarean delivery, possibly related to the increased use of combination antiretroviral drug regimens in the second report *[9]*. At the current time, decisions concerning mode of delivery in HCV/HIV-coinfected pregnant women should be based on HIV considerations alone (see **Intrapartum Care**).

Infants born to women with HCV/HIV coinfection should be assessed for HCV infection by HCV RNA virologic testing between 2 and 6 months of age (at least two negative tests are needed to exclude HCV infection because HCV viremia can be intermittent) and/or testing for anti-HCV antibody after age 15 months *[10]*.

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Stopping Antiretroviral Therapy during Pregnancy

Panel's Recommendations:

- ***If an antiretroviral drug regimen is stopped acutely for severe or life-threatening toxicity or severe pregnancy-induced hyperemesis unresponsive to anti-emetics, all drugs should be stopped at the same time and reinitiated at the same time (AIII).***
- ***If an antiretroviral drug regimen is stopped electively and the patient is receiving an NNRTI drug, consideration should be given to either (1) stopping the NNRTI first and continuing the other antiretroviral drugs for a period of time or (2) switching from an NNRTI to a PI prior to interruption and continuing the PI with the other antiretroviral drugs for a period of time before electively stopping. The optimal interval between stopping an NNRTI and the other antiretroviral drugs is not known; at least 7 days is recommended. Given the potential for prolonged detectable NNRTI concentrations for more than 3 weeks in patients receiving efavirenz-based therapy, some experts recommend continuing the other antiretroviral agents or substituting a PI plus two other agents for up to 30 days (CIII).***
- ***If nevirapine is stopped and more than 2 weeks have passed prior to restarting therapy, nevirapine should be restarted with the 2-week dose escalation period (AII).***

Discontinuation of antiretroviral drug regimens during pregnancy may be indicated in some situations including serious drug-related toxicity, pregnancy-induced hyperemesis, acute illnesses or planned surgeries that preclude oral intake, lack of available medication, or patient request.

Continuation of all drugs during the intrapartum period is generally recommended. Women who are having an elective cesarean section can take oral medications prior to the scheduled surgery and restart drugs following

surgery. Given that most drugs are given once or twice daily, the woman would either not miss any doses or at most receive the postpartum dose a few hours late.

When short-term drug interruption is indicated, in most cases, all antiretroviral drugs should be stopped and reintroduced at the same time. This can be problematic with drugs that have a long half-life. However, in conditions such as severe or life-threatening toxicity or severe pregnancy-induced hyperemesis unresponsive to anti-emetics, the clinician has no choice but to stop all therapy at the same time.

NNRTI drugs like nevirapine and efavirenz have very long half-lives and can be detected for 21 days or longer after discontinuation; efavirenz has a longer half-life than nevirapine *[1-5]*. As the other drugs with shorter half-lives are cleared, only the NNRTI drug may persist, resulting in persistent subtherapeutic drug levels that can increase the risk of selection of NNRTI-resistant mutations. In addition, it is known that certain genetic polymorphisms may result in slower rate of clearance. These polymorphisms may be more common among some ethnic groups, such as in African Americans and in Hispanics *[3, 5]*. To prevent prolonged exposure to a single drug, some experts recommend stopping the NNRTI first and continuing the other antiretroviral drugs for a period of time *[2]*. However, the optimal interval between stopping an NNRTI and the other antiretroviral drugs is not known; detectable levels of NNRTIs may be present from less than 1 week to greater than 3 weeks after discontinuation (the longer duration is primarily observed with efavirenz) *[5]*. An alternative strategy is to substitute a PI for the NNRTI and to continue the PI with dual NRTIs for a period of time. In a post-study analysis of the patients who interrupted therapy in the SMART trial, patients who were switched from an NNRTI to a PI-based regimen prior to interruption had a lower rate of NNRTI-resistant mutation after interruption and a greater chance of resuppression of HIV-RNA after restarting therapy than those who stopped all the drugs simultaneously or stopped the NNRTI before the dual-NRTIs *[6]*. The optimal duration needed to continue either dual nucleosides or the substituted PI-based regimen after stopping the NNRTI is not known; at least 7 days is recommended based on studies to reduce resistance following single-dose nevirapine *[7]*. With efavirenz use, there is the potential of prolonged detectable NNRTI concentrations for more than 3 weeks; therefore some suggest if stopping efavirenz-based therapy, the dual nucleosides or PI may need to be continued for up to 30 days. Further research is needed to assess appropriate strategies for stopping NNRTI-containing combination regimens.

An additional consideration is reintroduction of nevirapine if it is temporarily stopped for some reason and subsequently restarted. Currently, a 2-week, half-dose escalation is recommended in patients who are started on nevirapine. Dose escalation is necessary because nevirapine induces its own metabolism by inducing CYP3A4 liver metabolic enzymes; thus, initial administration of the full therapeutic dose will result in elevated drug levels until metabolic enzyme induction has occurred. In cases where nevirapine has been discontinued for more than 2 weeks, it is recommended that another 2-week dose escalation be used when it is reintroduced.

Failure of Viral Suppression

Panel's Recommendations:

- ***If there is failure of viral suppression after an adequate period of treatment:***
  - ***Assess resistance and adherence (AII).***
  - ***Consult an expert in the care of HIV-infected adults (AIII).***
- ***Scheduled cesarean delivery is recommended for HIV-infected pregnant women who have HIV RNA levels >1,000 copies/mL near the time of delivery (AII).***

The management of women on chronic antiretroviral therapy who have suboptimal suppression of HIV RNA (i.e., detectable virus at any time during pregnancy) should include evaluation for resistant virus, assessment of adherence, incorrect dosing or potential problems with absorption (e.g., with nausea/vomiting or lack of attention to food requirements), and consideration of modification of antiretroviral therapy. Experts in the care

of antiretroviral-experienced adults should be consulted, in particular when a change in drug regimen is necessary.

HIV RNA levels should be assessed 2 to 6 weeks following initiation or change of antiretroviral drug regimen to provide an initial assessment of efficacy *[8]*. Baseline HIV RNA levels have been shown to affect the time course of response in pregnant as well as nonpregnant individuals *[9]*. Most patients with an adequate viral response at 24 weeks have had at least a 1 $\log_{10}$ copies/mL HIV RNA decrease by 1 to 4 weeks after starting therapy *[8]*. Treatment-naïve individuals should have HIV RNA <400 copies/mL after 24 weeks of treatment and <50 copies/mL after 48 weeks of treatment.

Because maternal antenatal viral load correlates with risk of perinatal HIV transmission, suppression of HIV RNA to undetectable levels should be achieved as rapidly as possible. Scheduled cesarean delivery is recommended for HIV-infected pregnant women who have HIV RNA levels >1,000 copies/mL near the time of delivery (see **Transmission and Mode of Delivery**).

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